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Childhood trauma and being at-risk for psychosis are associated with higher peripheral endocannabinoids

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Original Article

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Abstract

Background. Evidence has been accumulating regarding alterations in components of the endocannabinoid system in patients with psychosis. Of all the putative risk factors associated with psychosis, being at clinical high-risk for psychosis (CHR) has the strongest association with the onset of psychosis, and exposure to childhood trauma has been linked to an increased risk of development of psychotic disorder. We aimed to investigate whether being at-risk for psychosis and exposure to childhood trauma were associated with altered endocannabinoid levels.

Method. We compared 33 CHR participants with 58 healthy controls (HC) and collected information about previous exposure to childhood trauma as well as plasma samples to analyse endocannabinoid levels.

Results. Individuals with both CHR and experience of childhood trauma had higher *N*-palmitoylethanolamine ($p < 0.001$) and anandamide ($p < 0.001$) levels in peripheral blood compared to HC and those with no childhood trauma. There was also a significant correlation between *N*-palmitoylethanolamine levels and symptoms as well as childhood trauma.

Conclusions. Our results suggest an association between CHR and/or childhood maltreatment and elevated endocannabinoid levels in peripheral blood, with a greater alteration in those with both CHR status and history of childhood maltreatment compared to those with either of those risks alone. Furthermore, endocannabinoid levels increased linearly with the number of risk factors and elevated endocannabinoid levels correlated with the severity of CHR symptoms and extent of childhood maltreatment. Further studies in larger cohorts, employing longitudinal designs are needed to confirm these findings and delineate the precise role of endocannabinoid alterations in the pathophysiology of psychosis.

Introduction

Independent of evidence associating cannabis use and onset and relapse of psychosis (Moore *et al.*, 2007; Schoeler *et al.*, 2016*a*, 2016*b*, 2016*c*; Sami and Bhattacharyya, 2018), evidence has also been accumulating regarding alterations in components of the eCB system in patients with psychosis (Bioque *et al.*, 2013; Ranganathan *et al.*, 2016). The endocannabinoid (eCB) system is a lipid signalling system that is involved in the regulation of brain development, motor control, cognition, emotional responses, and homeostasis. The most researched endocannabinoids (eCBs), which are the endogenous ligands for cannabinoid receptors (particularly CB1 and CB2), are anandamide (AEA) and 2-arachidonoylglycerol (2AG), while there are also the structurally analogous lipids *N*-palmitoylethanolamine (PEA) and *N*-oleoylethanolamine (OEA). A number of studies have investigated eCB levels in peripheral blood samples, because of easy accessibility and found that AEA is increased in schizophrenia patients and that clinical remission is associated with a decrease in AEA (De Marchi *et al.*, 2003; Reuter *et al.*, 2017; Koethe *et al.*, 2018). Studies investigating levels in cerebrospinal fluid (CSF) have also found alterations in the eCB system (Giuffrida *et al.*, 2004). For example, compared to healthy controls, AEA was increased in the CSF of people with early psychosis, with higher AEA levels being linked to the delayed transition to psychosis in those in the prodromal phase of the illness, suggestive of a protective role for AEA in psychosis (Koethe *et al.*, 2009). Table 1 summarises current evidence of eCB alteration in those with established psychosis (Leweke *et al.*, 1999; De Marchi *et al.*, 2003; Giuffrida *et al.*, 2004; Leweke *et al.*, 2007; Reuter *et al.*, 2017; Koethe *et al.*, 2018) or at risk (Koethe *et al.*, 2009). In general, these studies suggest higher

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Table 1. Studies investigating eCB levels in blood and CSF in patients *v.* controls

Author	Participants (n); Diagnosis	Antipsychotic treatment	Cannabis use	Findings
Studies with blood				
De Marchi *et al.* (2003)	12 patients with schizophrenia 20 healthy volunteers	No medication 30 days prior to the study	No abuse of cannabis in the year preceding the study	AEA significantly higher in patients (7.79 ± 0.50 pmol/ml) compared to controls (2.58 ± 0.28 pmol/ml) $p = 0.16$. Clinical remission was associated with lower levels of AEA and of the mRNA transcripts for CB2 receptors and FAAH
Giuffrida *et al.* (2004)¥	47 schizophrenia patients (P) 84 healthy controls (HC) 13 dementia patients (P) 22 affective disorder patients (P)	Antipsychotic naïve Medication free Pharmacological treatment Pharmacological treatment	P – No specific information, but cannabis use in patients reported to be similar to that of the healthy controls HC – 57 lifetime frequency of cannabis use of up to 5 times, but not within the last 12 months before inclusion into the study. 27 lifetime cannabis use of 20 to 50 times but not within the last 6 months prior to the study	Anti-psychotic naïve schizophrenia patients: AEA = 0.651 ± 0.140 pmol/ml, healthy controls: AEA = 0.427 ± 0.071 pmol/ml, $p = 0.380$
Koethe *et al.* (2009)*	27 prodromal patients 81 healthy controls	No cannabis use 6 weeks prior to study 55 controls (68%) had taken cannabis <20 times/lifetime and 26 (32%) had used cannabis >20 but <50 times/lifetime	8 received medication	Patients AEA levels: (0.216 pmol/ml IQR < 0.001 to 0.515) controls AEA levels: (<0.001 pmol/ml IQR < 0.001 to 0.005) $p = 0.838$
Koethe *et al.* (2018)	25 pairs of monozygotic twins discordant for schizophrenia, 14 pairs of monozygotic twins discordant for bipolar disorder, 8 pairs of healthy control monozygotic twins	13 twin pairs reported using cannabis in the past, recent cannabis use only reported by one twin pair	No relationship between eCBs and medication found	Twins discordant for schizophrenia or bipolar disorder had higher levels of AEA (Affected twin: median 6.31 pmol/ml, non-affected twin: median 6.57 pmol/ml, $p = 0.0833$) and PEA (affected twin: 21.18 pmol/ml, non-affected twin: 23.26 pmol/ml, $p = 0.264$) compared to healthy twins (Median AEA = 4.33 pmol/ml $p = 0.002$, Median PEA 2.85, $p < 0.001$). Non-affected twins discordant for schizophrenia, who developed a psychotic disorder within 5 years follow-up showed lower AEA and 2-AG than twins who remained healthy
Reuter *et al.* (2017)+	28 first episode schizophrenia patients, 81 healthy controls	Schizophrenia patients had higher cannabis use history than HC. Cannabis use controlled for in analyses and had no effect on AEA	Medication naïve	No difference in serum AEA

(*Continued*)

Table 1. (*Continued.*)

Author	Participants (n); Diagnosis	Antipsychotic treatment	Cannabis use	Findings
Studies with CSF				
Leweke *et al*. (1999)	10 psychosis patients 11 healthy controls	5 patients medication naïve, 2 no medication for 7 days, 3 on antipsychotics	4 patients had a history of intermittent consumption of cannabis resin	Elevated levels of AEA (0.70 ± 0.47 pmol/ml) and PEA (3.50 ± 1.73 pmol/ml) in patients compared to controls (AEA = 0.30 ± 0.29 pmol/ml, PEA = 1.80 ± 0.83 pmol/ml) $p = 0.05$
Giuffrida *et al*. (2004)¥	See above	See above	See above	AEA higher in anti-psychotic naïve schizophrenia patients (0.057 ± 0.011 pmol/ml) compared to other patients and controls (0.007 ± 0.002 pmol/ml) $p = 0.000$ and correlated with psychotic symptoms ($p = 0.001$). This elevation was not seen in those treated with typical antipsychotics (0.031 ± 0.012 pmol/ml) but was in those treated with atypical antipsychotics (0.062 ± 0.016 pmol/ml). OEA levels similar in control and antipsychotic naïve schizophrenia patients. PEA lower in antipsychotic naïve patients (3.441 ± 0.494, $p = 0.017$) compared to controls (5.282 ± 0.554)
Leweke *et al*. (2007)	47 first episode psychosis patients 81 healthy controls	25 low frequency users (LFU) (defined as less than 5 times in a lifetime), 19 high frequency users (HFU) (defined as more than 20 times) 55 LFU 26 HFU	Antipsychotic naïve	First episode psychosis low frequency cannabis users had higher AEA levels than high frequency users ($p = 0.008$) and healthy controls LFU: ($p < 0.001$); HFU: ($n = 26$, $p < 0.001$)
Koethe *et al*. (2009)*	See above	See above	See above	Patients had higher AEA levels (0.006 pmol/ml IQR < 0.001 to 0.073) than controls (<0.001 pmol/ml IQR < 0.001 to 0.005) $p = 0.004$. Patients who had lower levels transitioned earlier ($p = 0.095$)
Reuter *et al*. (2017)+	See above	See above	See above	CSF AEA higher in patients (0.032 ± 0.042 pmol/ml) compared to controls (0.008 ± 0.015 pmol/ml) $p < 0.001$

*+¥ These studies are the same, but used both serum and CSF eCB.

levels of AEA in patients, with one study also reporting higher levels of PEA (Koethe *et al*., 2018). More recently, PET imaging evidence has also emerged of reduced CB1 availability in patients with established psychosis (Ranganathan *et al*., 2016; Borgan *et al*., 2018) with prominent reductions in key brain regions implicated in psychosis, consistent with post-mortem evidence (Eggan *et al*., 2008; Eggan *et al*., 2010; Volk *et al*., 2014). However, evidence from other PET and post-mortem studies has not always been consistent (Wong *et al*., 2010; Ceccarini *et al*., 2013), potentially due to methodological differences between studies. Nevertheless, existing evidence reviewed above suggests that eCB dysfunction may be linked to the pathophysiology of psychotic disorders such as schizophrenia (Leweke *et al*., 2016; Ranganathan *et al*., 2016).

Therefore, the objective of the present study was to investigate whether established risk factors of psychosis are associated with evidence of eCB dysfunction as indexed by eCB levels in peripheral blood.

Endocannabinoid system and clinical high-risk state for psychosis

Out of all the putative risk factors associated with the onset of psychosis, a recent umbrella review incorporating data from 683 individual studies investigating 170 different risk or protective factors, showed that clinical high-risk for psychosis state (CHR) has the strongest association with the onset of psychosis (Radua *et al*., 2018). Therefore, whether presentation with the CHR state is associated with evidence of eCB dysfunction is of particular interest. To our knowledge, only one study has examined eCB levels in those at CHR for psychosis (Koethe *et al*., 2009). Presented in Table 1, this study examined 27 patients in the initial prodromal state of psychosis and 81 healthy volunteers. They found that CSF AEA levels were elevated in the patients and that those with lower levels had a higher risk for transitioning to psychosis, although there was no significant difference in serum AEA levels between those in the prodrome and healthy volunteers.

Endocannabinoid system and stress

Among the other recognised risk factors for psychosis (Radua *et al*., 2018), stress is ubiquitous, and our understanding of its role in enhancing the risk of mental disorders is increasingly becoming more sophisticated (Pruessner *et al*., 2017). It is also of considerable interest because its effects may be potentially amenable to treatment. Of the different types of stress, exposure to childhood trauma (CT) in particular has been linked to an increased risk of development of psychotic disorder (Read, 1997; Read *et al*., 2005; Varese *et al*., 2012) as well as its relapse (Petros *et al*., 2016). CT has also been shown to be a risk factor across the psychosis continuum with it being associated with an increase in psychotic-like symptoms in healthy controls (Fisher *et al*., 2012), as well as CHR (Bechdolf *et al*., 2010; Addington *et al*., 2013) and higher paranoia (Appiah-Kusi *et al*., 2017).

A significant body of evidence has amassed which indicates that the eCB system is intimately involved in the regulation of the stress response (Hill and Tasker, 2012). *In vitro* studies using rat tissue showed that the eCB system was involved in feedback control of the HPA axis response (Di *et al*., 2003) and that glucocorticoids could in turn induce rapid increases in AEA and 2-AG (Di *et al*., 2005*a*).

In human studies, it has been reported that acute stress leads to an increase in circulating eCBs and structurally similar lipids (Hill *et al*., 2009; Dlugos *et al*., 2012). Furthermore, animal (Di *et al*., 2005*b*; Malcher-Lopes *et al*., 2006) as well as human studies have shown that increased glucocorticoids, the key stress response hormone, cause an elevation in eCB levels (Dlugos *et al*., 2012).

While the relationship between acute exposure to stress and alterations in the eCB system has been investigated a great deal, particularly in animal studies, whether exposure to specific types of stress, such as childhood trauma, a known risk factor for psychosis, is associated with altered functioning of the eCB system in humans remains unclear.

As outlined above and argued previously (Mizrahi, 2015; Appiah-Kusi *et al*., 2016), although there is some evidence that risk factors for the onset of psychosis such as the CHR state and childhood trauma may be associated with alterations in the eCB system, their association has not been systematically investigated to date. Therefore, the main objective of the present study was to investigate whether risk factors for psychosis, namely presentation with a CHR state and exposure to childhood trauma were associated with altered eCB levels as detected in peripheral blood and whether the co-occurrence of both risk factors had a greater effect on eCB levels. Specifically, we predicted that both being CHR and exposure to CT on their own would be associated with higher levels of AEA and PEA (e.g. Koethe *et al*., 2018) and that individuals with both risk factors (i.e. CHR and exposed to CT) would exhibit the greatest alteration in eCB levels. Further we predicted that the severity of symptoms of CHR and the total childhood trauma score would correlate with AEA and PEA levels.

Method

Participants

Cases consisted of 33 individuals who met the criteria for Personal Assessment and Crisis Evaluation (PACE) CHR criteria (Yung *et al*., 1998), who were recruited from a specialist clinical service for people at risk for psychosis in South London who were enrolled on a clinical trial, all procedures reported here were carried out before any drugs were administered. Inclusion criteria and sampling procedures have been reported previously (Bhattacharyya *et al*., 2018). Individuals were included if they met CHR criteria and were aged 18–35 and agreed to stay abstinent from drugs for the duration of the study. Individuals were excluded if there was a history of previous psychotic disorder or manic episode, neurological disorder or current DSM-IV diagnosis of substance dependence, IQ less than 70 and any contraindication to MRI or treatment with CBD. Controls consisted of 58 individuals who were recruited via classified advertisement and community websites from the same geographical area as those at CHR. All participants were matched for age (within 3 years) and gender. All procedures complied with the Helsinki Declaration, as revised in 2008. Participants were reimbursed for their time and travel expenses. These procedures were approved by Psychiatry, Nursing and Midwifery Research Ethics Committee at King's College, London (Approval number PNM/13/14-22) and NHS ethics (13/LO/0243). All participants gave written informed consent before taking part in the study and completed anonymised questionnaires in private.

Assessment of childhood trauma

Childhood trauma was assessed using the Childhood Trauma Questionnaire (CTQ) (Bernstein and Fink, 1998). The CTQ is a

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28-item self-report questionnaire that retrospectively assesses CT and provides scores on five subscales (emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect) as well as a total trauma score produced by summing all 5 subscales. We used the cut-off points outlined by Walker *et al.* (1999) to create two groups; maltreatment and no maltreatment (Walker *et al.*, 1999). The cut-off points were 8 for physical abuse, sexual abuse and physical neglect, 15 for emotional neglect and 10 for emotional abuse. Anyone who scored at or above the cut-off point for any of the five subscales were placed in the maltreatment group, and those below these cut-off points were placed in the no maltreatment group.

Assessment of perceived stress

Perceived stress was assessed using the Perceived Stress Scale (PSS) (Cohen *et al.*, 1983). The PSS is a 14-item scale, which assesses the degree to which participants feel their life is stressful. They are asked to report on stressful experiences within the last month and in particular situations in which one might feel that life is unpredictable, uncontrolled and overloaded.

Assessment of symptoms in CHR

Symptoms were assessed using the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung *et al.*, 2005). This is a semi-structured interview which assesses disorders of thought content, perceptual abnormalities, conceptual disorganisation, motor changes, concentration and attention, emotion and affect, subjectively impaired energy and impaired tolerance to stress. This was conducted by an experienced psychiatrist (RW).

Cannabis use assessment

Cannabis use was assessed using the Cannabis Experiences Questionnaire (CEQ) (Barkus *et al.*, 2006), a 17-item self-report questionnaire. For the purpose of this study, we used the variable which indicated if they had current cannabis use.

Endocannabinoid analysis

On the study day, participants arrived for their assessment at 9am. Following a standardised breakfast, blood samples were collected at 10.30 AM. 26 CHR participants and 46 healthy controls were able to provide blood samples for analysis. Samples were immediately processed, and the plasma stored at −80 °C until analysis. Endocannabinoid levels were assayed using a standardised Liquid Chromatography-Mass Spectrometry (LC-MS) technique using Waters Xevo TQS-micro coupled to a UHPLC Acquity H Class LC system at King's College London.

Analysis

Data analysis was carried out using IBM SPSS Statistics 21 (SPSS, 2012). Missing values on the questionnaires were imputed by replacing them with individual participants' mean score for the scale. Six participants missed one question each on the CTQ and one participant missed one question on the PSS. Six healthy controls and 1 CHR participant did not complete the CTQ, two healthy controls did not complete the PSS. Therefore, the analyses were conducted after imputing the values of CTQ and PSS for individuals with missing data. We compared whether sociodemographic variables and potential confounders (cannabis use, perceived stress, age and gender) were different between either the HC or CHR or were significantly associated with eCB levels on univariate analyses using chi-square tests or *t* tests. Those confounders that were significantly different were controlled for in subsequent analyses. Four separate factorial analyses of covariance (ANCOVAs) were carried out to investigate whether exposure to CT and being CHR were associated with higher levels of AEA, PEA, 2AG and OEA, with eCB levels being the dependent variable, presence or absence of risk factors such as being CHR (or not) and having been exposed to CT (or not) being the two independent variables and PSS score as the covariate. Finally, we created a new variable, creating three groups: (1) those that were both CHR and had a history of CT; (2) those that were CHR but had no history of CT or HC with a history of CT; and (3) HC without a history of CT. We then conducted two separate ANCOVAs to assess if those with both of these risk factors (being CHR and exposed to CT) had higher eCB levels than those with only one of these risk factors (i.e. those that were CHR but had no history of CT or those HC with a history of CT). We also tested whether eCB levels were highest in those who were both CHR and had a history of CT and lowest in HC without a history of CT, with intermediate levels in the group that comprised those that were CHR but had no history of CT and those HC with a history of CT. Finally, we conducted separate correlational analyses to investigate whether AEA and PEA levels were associated with symptoms in the CHR group or with the total childhood trauma score.

Table 2. Demographics

	CHR ($n = 33$)	HC ($n = 58$)	*P*
Gender (% female)	49	47	0.76
Current cannabis use (% yes)	42.4	41.5	0.93
Age (M, S.D.)	23.82, 5.28	25.05, 4.9	0.27
PSS (M, S.D.)	30.47, 6.20	25.21, 7.00	0.001
CT (% yes)	81.8 ($n = 32$)	53.4 ($n = 52$)	0.03

Results

Table 2 summarises the participants' demographic and clinical information. There were no statistically significant differences in age, gender or current cannabis use across the diagnostic groups. PSS and CTQ scores were higher in CHR compared to HC.

Table 3 outlines that on univariate analysis, neither previous cannabis use nor gender was associated with statistically significant effects on eCB levels in either the HC or CHR except AG2 in HC. Age had no effect on eCB levels, and 2AG only was significantly related to PSS levels.

Table 4 shows that CHR had significantly higher OEA, AEA and 2AG levels compared to HC and approached significance for PEA.

Table 5 summarises the mean (S.D.) levels of the different eCBs in people with CHR or exposed to CT, while controlling for PSS score. We did not control for other potential confounding factors such as gender or history of previous exposure to cannabis as these factors were not significantly associated with eCB levels, consistent with previous evidence (Giuffrida *et al.*, 2004; Koethe

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Table 3. Effect of cannabis use and gender on eCB levels

	HC (M, S.D.) $n = 34$		CHR (M, S.D.) $n = 26$		p	
Cannabis use	Yes ($n = 15$)	No ($n = 19$)	Yes ($n = 9$)	No ($n = 16$)	HC	CHR
AEA	1.37, 0.69	1.12, 0.50	1.99, 0.83	2.04, 1.32	0.21	0.51
2AG	3.43, 2.07	2.07, 1.08	10.30, 9.322	4.90, 2.76	0.05	0.76
PEA	10.43, 4.05	8.64, 3.82	13.16, 9.14	14.38, 10.18	0.20	0.92
OEA	2.92, 1.42	2.41, 1.55	4.44, 2.28	3.80, 2.33	0.33	0.12
Gender	Male ($n = 26$)	Female ($n = 20$)	Male ($n = 12$)	Female ($n = 13$)		
AEA	1.40, 0.70	1.18, 0.54	1.70, 1.22	2.36, 1.03	0.26	0.15
2AG	2.99, 1.80	2.84, 1.99	5.96, 6.47	7.57, 6.26	0.79	0.52
PEA	10.82, 4.63	9.22, 3.96	11.95, 9.25	15.97, 10.02	0.22	0.30
OEA	2.91, 1.37	2.88, 1.85	3.28, 2.46	4.72, 1.96	0.95	0.12
Age	b	S.E. B	β	R^2	p	
AEA	−0.39	0.64	−0.07	0.005	0.55	
2AG	−0.13	0.13	−0.12	0.01	0.34	
PEA	−0.01	0.09	−0.02	0.000	0.88	
OEA	−0.33	0.31	−0.13	0.02	0.29	
PSS						
AEA	0.65	0.941	0.08	0.01	0.49	
2AG	0.45	0.189	0.273	0.08	0.02	
PEA	0.06	0.13	0.06	0.004	0.61	
OEA	0.21	0.45	0.06	0.003	0.65	

Table 4. Descriptive statistics

	CHR ($n = 26$)	HC ($n = 46$)	t	df	p
OEA ng/ml (M, S.D.)	4.03, 2.29	2.9, 1.58	−2.1	36.7	0.034
PEA ng/ml (M, S.D.)	13.96, 9.67	10.12, 4.38	−1.92	30.9	0.07
AEA ng/ml (M, S.D.)	2.03, 1.16	1.3, 0.64	−2.94	33.89	0.006
2AG ng/ml (M, S.D.)	6.77, 6.29	2.92, 1.87	−3.04	27.51	0.005

et al., 2009; Reuter *et al.*, 2017). Exposure to CT was associated with significantly higher levels of PEA, AEA and 2AG while CHR patients had significantly higher levels of AEA and 2AG in peripheral blood. Furthermore, there was a statistically significant effect of interaction between CT and CHR on PEA levels and a trend level effect on AEA levels in peripheral blood.

Table 6 shows that individuals with one risk factor (either HC with a history of CT or CHR with no history of CT) had lower eCB levels than individuals with both risk factors (those who were CHR and had a history of CT).

Further post hoc analysis (presented in Table 7) revealed that eCB levels were highest in those who were both CHR and had a history of CT and lowest in HC without a history of CT, with intermediate levels in the group that comprised those that were CHR but had no history of CT and those HC with a history of CT.

There was a significant correlation between PEA levels and total CAARMS score ($r = 0.44$, $p = 0.03$) and total CTQ score ($r = 0.28$, $p = 0.02$). There was a trend for correlation between AEA levels and total CAARMS score ($r = 0.34$, $p = 0.09$) but not with total CTQ score.

Discussion

As predicted, we found that CHR individuals had significantly higher AEA levels, but unlike previous studies, we also found higher OEA and 2AG levels. Contrary to previous studies (Leweke *et al.*, 1999; Koethe *et al.*, 2018), we did not find significantly higher PEA levels, although this difference did approach significance. This is in line with evidence that schizophrenia patients had higher blood levels of AEA (De Marchi *et al.*, 2003) and that those in the prodromal state of psychosis had higher CSF levels of AEA (Koethe *et al.*, 2009). Our study extends previous research by showing that those with a history of childhood maltreatment also had higher levels of AEA, 2AG and PEA. Furthermore, we report evidence of an effect of interaction between CHR and CT on PEA levels, such that in the absence of exposure to CT, CHR status was associated with lower levels of PEA compared to HC, while those who were both CHR and had been exposed to CT had higher levels of PEA compared to those who either had none of these risk factors or had one risk alone. Additional analyses showed that, as predicted, those with only one risk factor (exposure to CT or CHR status) had lower levels of PEA, AEA, OEA and 2AG compared to those with both risk factors (CHR with history of exposure to CT).

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Table 5. ANCOVA results

CT	HC ($n = 43$)	CHR ($n = 25$)	ANCOVA	$F_{(1, 63)}$	p
OEA					
Yes	3.05 (1.78)	4.43 (2.05)	Diagnosis	2.18	0.15
			CT	3.58	0.07
No	2.71 (1.26)	2.80 (3.03)	Diagnosis × CT	1.64	0.21
			PSS	3.47	0.07
PEA					
Yes	10.29 (4.69)	15.94 (8.95)	Diagnosis	1.88	0.18
			CT	5.47	0.02
No	9.74 (3.53)	8.47 (10.40)	Diagnosis × CT	4.10	0.05
			PSS	4.08	0.05
AEA					
Yes	1.36 (0.67)	2.26 (1.15)	Diagnosis	5.10	0.03
			CT	6.43	0.01
No	1.20 (0.53)	1.30 (0.92)	Diagnosis × CT	3.39	0.07
			PSS	3.58	0.06
2AG					
Yes	3.47 (2.18)	7.79 (6.83)	Diagnosis	6.57	0.01
			CT	5.62	0.02
No	2.24 (1.09)	3.70 (1.52)	Diagnosis × CT	1.73	0.19
			PSS	1.5	0.22

Table 6. Comparison of 1 risk factor to 2 risk factors

	M	S.D.	$F_{(1,49)}$	p
OEA				
1 risk factor	3.01	1.92	6.16	0.02
Both risk factors	4.28	2.05		
PEA				
1 risk factor	10.00	5.76	8.37	0.006
Both risk factors	15.94	8.95		
AEA				
1 risk factor	1.35	0.69	12.51	0.001
Both risk factors	2.26	1.15		
2AG				
1 risk factor	3.51	2.07	10.74	0.002
Both risk factors	7.79	6.83		

Further, eCB levels increased linearly with the number of risk factors individuals were exposed to, such that those who were exposed to neither risk factor (HC without CT) had lower eCB levels compared to those with only one risk factor (exposure to CT or CHR status), who in turn had lower levels compared to those with both risk factors (CHR with history of exposure to CT). Importantly, these results were not confounded by the effect of perceived stress as a result of recent stress exposure over the past month. Furthermore, we found a significant correlation between PEA levels and total CAARMS score as well as total CTQ score and a trend-level correlation between AEA and total CAARMS score. Collectively, these results suggest that altered levels of these eCBs may be related to the extent of exposure to risk (as indexed by the severity of the CHR symptoms in those with CHR as well as the total CTQ score in those exposed to trauma in childhood), supporting the idea that their alterations may be linked to the risk of developing psychosis and potentially suggesting how stress may increase the risk of psychosis.

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Table 7. Linear relationship between eCB levels and number of risk factors

	M	S.D.	$F_{(2,71)}$	p
OEA				
No risk factors	2.63	1.31	7.11	0.002
1 risk factor	3.01	1.92		
Both risk factors	4.28	2.05		
PEA				
No risk factors	9.51	4.36	8.16	0.001
1 risk factor	10.00	5.76		
Both risk factors	15.94	8.95		
AEA				
No risk factors	1.21	0.60	11.93	<0.001
1 risk factor	1.35	0.69		
Both risk factors	2.26	1.15		
2AG				
No risk factors	2.17	0.99	12.83	<0.001
1 risk factor	3.51	2.07		
Both risk factors	7.79	6.83		

These results are consistent with evidence from Koethe *et al.* (2018), who reported higher levels of AEA and PEA in affected twins discordant for schizophrenia or bipolar disorder compared to healthy twins and also Leweke *et al.* (1999) who also reported elevated levels of AEA and PEA in patients with schizophrenia. In contrast, Giuffrida *et al.* (2004) reported lower levels of PEA in antipsychotic naïve schizophrenia patients compared to controls. Previous studies have reported a negative association between AEA levels and severity of psychotic symptoms in those with established psychosis (Giuffrida *et al.*, 2004) which is in contradiction to our results. Methodological differences between our study and previous ones may underlie these differences. In particular, Giuffrida *et al.* examined CSF and studied patients with a diagnosis of schizophrenia whereas we examined eCB levels in peripheral blood and studied people who had not yet developed a frank psychotic disorder. Furthermore, others have reported lower levels in those in clinical remission (De Marchi *et al.*, 2003), consistent with the results presented here.

How eCB dysfunction as indicated by altered eCB levels may lead to psychosis remains unclear. It has been suggested that dysfunction of the eCB system may lead to psychosis by increasing dopaminergic activity (Müller-Vahl and Emrich, 2008), the final common pathway in the pathophysiology of psychosis (Howes and Kapur, 2009). Preclinical studies have demonstrated that administration of a dopamine receptor agonist is associated with increase in AEA release in the dorsal striatum (Giuffrida *et al.*, 1999) and hyperdopaminergia observed in dopamine transporter knockout mice (an animal model for schizophrenia) is associated with decrease in striatal AEA levels (Tzavara *et al.*, 2006).

Strengths and limitations

The present study has a number of limitations. One of the key limitations of the present study relates to its cross-sectional design, thus limiting any conclusions that may be drawn about the relationship between CHR status and exposure to CT and alterations observed in eCB levels as well as between eCB alterations and psychosis. In particular, it is not possible to disentangle whether heightened eCB levels are a response to the illness or play a causal role in the development of psychosis. Longitudinal studies that include baseline eCB level assays that predated exposure to CT or the label of CHR status are ideal to help infer whether alterations predated risk status, but are logistically demanding and were not available in the present study. Follow-up studies in larger cohorts are needed to investigate the association between altered eCB levels and later transition to psychosis in order to understand the precise nature of the relationship between alterations observed and the onset of psychosis. Nevertheless, results presented here support a role for eCB alterations in the pathophysiology of psychosis.

We asked all participants to refrain from the use of drugs particularly cannabis before the study and recent cannabis exposure was ruled out by urine drug screen, which confirmed that participants were drug-free on the study day. Nevertheless, we cannot fully rule out enduring changes to the eCB system as a result of long-term cannabis use affecting the results of the present study. However, this seems less likely as we did not find even a trend-level association between history of recent cannabis use and eCB levels in our study participants. Furthermore, negative results on urine drug screen implied that study participants must have been abstinent from cannabis for more than a few days before taking part in the study and recent evidence suggests that other parameters of eCB function such as brain CB1 receptor availability start returning back to normal as early as after 2 days of abstinence (D'Souza *et al.*, 2016).

Detection of altered eCB levels in peripheral blood samples in this study also raises the issue of whether alterations in peripheral blood are related to any changes in the brain and vice versa. In previous studies examining differences in eCB levels between

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patients and controls, studies investigating levels in CSF (Koethe *et al.*, 2009) have found similar results to those investigating peripheral blood levels (Leweke *et al.*, 2012), although other studies have reported no correlation between serum and CSF eCB levels (Koethe *et al.*, 2009; Reuter *et al.*, 2017). Nevertheless, it is worth noting that Reuter *et al.* (2017) reported that association between binocular depth inversion, a visual perceptual abnormality linked to psychosis vulnerability, and eCB (AEA) level alteration that differentiated schizophrenia patients from healthy controls, was observed in AEA levels in peripheral blood rather than in the CSF (Reuter *et al.*, 2017).

It may also be argued that although our study controlled for the confounding effects of perceived stress, we did not control for the effects of subsequent trauma exposure or re-victimisation following an initial exposure to trauma in childhood. While it is well known that those who experience trauma are more likely to experience re-victimisation in adulthood (Coid *et al.*, 2001), a recent study investigating 7353 people found that the association between childhood trauma and psychosis was not mediated by re-victimisation (Bebbington *et al.*, 2011), suggesting that effects of re-victimisation are unlikely to have confounded the results of the present study.

Notwithstanding these limitations, it is worth noting that we employed an internationally recognised definition of CHR unlike in the previous study investigating eCB abnormalities in prodromal psychosis patients (Koethe *et al.*, 2009) and also investigated all four major eCBs unlike in previous studies.

Implications and conclusions

In summary, here we have shown an association between CHR status and/or a history of childhood maltreatment and elevated eCB levels in peripheral blood, with a greater alteration in those with both CHR status and history of childhood maltreatment and a correlation between the altered levels and severity of CHR symptoms and extent of childhood maltreatment. However, further studies in larger cohorts and employing longitudinal design are needed to confirm these findings and delineate the precise role of eCB alterations in the pathophysiology of psychosis. If confirmed, this may complement preclinical evidence that point towards the eCB system as a potential target for mitigating the harmful effects of stress.

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